Does Clinical Evidence of Heterogeneity Impact Treatment Selection? A Case Study of Abiraterone for Metastatic Prostate Cancer

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ABSTRACT

Background: Two pivotal randomized controlled trials (RCTs) demonstrate that abiraterone acetate + prednisone (AAP) combined with androgen deprivation therapy (ADT) significantly extends the survival of men with metastatic hormone-sensitive prostate cancer (mHSPC) compared with ADT alone. Their subgroup analyses indicate that the survival benefit is significant for younger men but not older men. We aimed to assess whether publication of the RCTs was associated with differential real-world AAP utilization by age groups. **Methods:** Using TriNetX electronic medical records data collected from 43 healthcare organizations across the United States, we performed a difference-in-differences event study among men with newly diagnosed mHSPC observed from June 2014 to June 2019. Eligible subjects were identified based on a comprehensive published algorithm. We analyzed the change in utilization rate of AAP before versus after publication of the RCTs among men aged <70 years versus ≥70 years, adjusting for demographic factors and clinical conditions. **Results:** Our study included 6,888 men with newly diagnosed mHSPC with 12,738 observations, of whom 46% were aged <70 years. The prepublication trends of AAP utilization were similar between the age groups, whereas publication of the RCTs was associated with a 3.5% higher adjusted uptake rate of AAP among younger men (95% CI, 1.2%–5.8%) relative to older men. This estimate reflects an uptake rate nearly 3 times higher than would have been expected had younger men followed the same utilization trends as older men. The estimates remained consistent throughout the postpublication period. **Conclusions:** Our study suggests that publication of the RCTs was associated with faster uptake of AAP among younger versus older men with newly diagnosed mHSPC, despite the absence of clinical guidance for differential treatment selection. This finding highlights the importance of confirmatory studies among older men, considering the uncertainties of subgroup analyses in RCTs.

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Background

In the era of evidence-based medicine, findings from large, well-designed randomized controlled trials (RCTs) form the foundation of medical evidence that should inform clinical guidelines and eventually translate into a change in clinical practice. Particularly in oncology, RCTs are the gold standard for evaluation of emerging treatments, providing a sound basis for the development of national guidelines, such as the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), and the subsequent adoption of new anticancer medicines.[1,2]

However, the mechanism and magnitude of clinical evidence translation into practice are uncertain and variable.[3] Previous studies attempted to understand the impact of RCT results on cancer treatment utilization. A prior study suggested that RCT results significantly increased anastrozole prescription for postmenopausal women with hormone receptor–positive early breast cancer.[4] Another study showed an increase in tamoxifen use after surgery for ductal carcinoma in situ following the release of RCT results, but the rates varied substantially across institutions.[5] These studies were limited to treatment pattern changes associated with the evidence of average treatment-related benefits or harms. Few studies have explored whether the evidence of treatment effect heterogeneity—usually found through subgroup analyses in RCTs—leads to differential cancer treatment utilization across subgroups. Informed by the evidence of such heterogeneity, it is appealing for clinicians to individualize treatment decisions according to relevant patient characteristics.[6]

Our study focused on the case of abiraterone acetate + prednisone (AAP) as a treatment for metastatic hormone-sensitive prostate cancer (mHSPC). Two pivotal phase III RCTs, LATITUDE[7] and STAMPEDE[8]—both released online in June 2017 by the *New England Journal of Medicine*—demonstrated that AAP combined with androgen deprivation therapy (ADT) significantly extended the survival of men with mHSPC compared with ADT alone. Furthermore,


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according to the subgroup analyses in both trials, the survival benefits of AAP were greater and statistically significant for younger compared with older men: the hazard ratio was not statistically significant for those aged ≥75 years in LATITUDE and aged ≥70 years in STAMPEDE. In addition to the RCTs, several meta-analyses of clinical trial data reached the same conclusion.[9–12] Nonetheless, there has been some controversy about whether the clinical evidence of age-based heterogeneity is well-established. Based on the current evidence, some researchers have suggested that age could be a factor to consider when making treatment decisions for mHSPC.[10,12–14] However, an argument against age-based treatment can be made due to the fact that the small sample size of older men in the clinical trials might render the subgroup-specific results unreliable.[9,15–17] Moreover, although the STAMPEDE trial presented a statistically significant interaction between age and treatment,[8] this was not clearly demonstrated in the LATITUDE trial.[7]

The promising findings from the RCTs successfully led to FDA approval[18] and an NCCN Guidelines recommendation[19] of AAP as a treatment for mHSPC, but the results of age subgroup analyses were not incorporated in the product label or clinical guidance. To date, it is still not clear whether the finding of age-based treatment effect heterogeneity might influence the real-world utilization of AAP despite the controversy about the evidence and the absence of relevant clinical guidance. Therefore, our study aimed to assess whether publication of the RCTs was associated with differential AAP uptake between younger (age <70 years) and older men (age ≥70 years) with mHSPC in the United States.

Methods

Data

We obtained electronic medical record (EMR) data from TriNetX (TriNetX, LLC), a collaborative research platform that collects administrative data from healthcare organizations (HCOs). The HCOs comprise hospitals, primary care, and specialty care and collect data from insured and uninsured individuals. Our analysis focused on data collected from 43 HCOs across the United States, including information on demographics, diagnoses, medications, procedures, and laboratory test results. More details about the TriNetX dataset can be found elsewhere.[20]

We defined the study population as men newly diagnosed with mHSPC in the United States. In accordance with a comprehensive, sensitive algorithm developed by Freedland et al,[21] we retrospectively identified an eligible cohort of men with mHSPC for analysis (details can be found in supplemental eTables 1–4, available with this article at JNCCN.org). The established first-line treatments for mHSPC include ADT alone and ADT combined with an add-on therapy (eg, AAP, docetaxel, or first-generation antiandrogen [taken for at least 3 months to avoid capturing antiandrogen used for flare control]; see supplemental eTable 5). First-line treatment was defined as ADT initiated within 3 months before or 12 months after the diagnosis of metastasis and before progression to hormone resistance.[22] Combination therapy was defined as an add-on therapy prescribed within 1 month before or 4 months after the ADT initiation date and before disease progression.[22] Those clinical definitions were drawn from previous literature and confirmed by a urologic oncology expert.

Our study assessed the uptake rate of first-line AAP; that is, the proportion of men with newly diagnosed mHSPC who initiated first-line AAP during a given period. The numerator of this proportion was the number of patients initiating first-line AAP during this period, and the denominator represented individuals at risk for initiating first-line AAP when entering this period. We first identified the numerator and denominator for a given 1-month period. Based on the aforementioned clinical definitions of first-line treatment and combination therapy, we established inclusion and exclusion criteria for the numerator and denominator (supplemental eTable 6). Due to the small sample size during each period, we further combined those numbers into 6-month periods for the analysis. We included all of the eligible observations from June 2014 (3 years before the publication) to May 2019 (2 years after the publication) and excluded those with missing data.

Variables

The outcome variable was a binary indicator for first-line AAP initiation during a given 6-month period. The primary independent variables included age group, time fixed effects, and their interactions. In LATITUDE[7] and STAMPEDE[8] trials, the cutoff ages for the subgroup analyses were 75 and 70 years, respectively. Conservatively, our analysis dichotomized the men into the age groups of ≥70 and <70 years. The fixed time effect variables indicated the 6-month periods before or after online publication of the 2 RCTs in June 2017, regarding the first period before the publication (ie, December 2016–May 2017) as the reference. The other covariates included race (African American/Black, White, Other), region (Northeast, Midwest, South, West), continuous age, number of metastatic sites, NCI Comorbidity Index (based on claims in the 12 months prior to the diagnosis of metastatic disease),[23] and presence of visceral or bone metastases.

Statistical Analysis

Primary Analysis

We conducted a retrospective difference-in-differences (DID) analysis to assess the differential utilization of AAP between age groups before versus after publication of the

RCTs. We used a linear generalized estimating equation (GEE) with an exchangeable correlation structure to account for within-subject correlation and a robust standard error estimator (statistical model provided in supplemental eAppendix 1).

The underlying assumption of the DID design is parallel trends, assuming that the trends in AAP usage between the 2 age groups would have remained the same in the absence of publication. With multiple time points before the clinical trial evidence publication, we assessed the assumption of parallel trends by visual inspection and jointly testing whether all of the coefficients of the interactions between age group and prepublication fixed time effects were equal to zero. If the assumption of parallel trends is met, the coefficients of the interactions for the postpublication periods will represent the adjusted DID estimate at each period (ie, the difference in uptake rate between the 2 groups during each postperiod relative to the difference during the reference period).

Secondary Analyses

We conducted 2 exploratory stratified analyses. The first analysis examined the association between the publication and age-based differential uptake of AAP stratified by comorbidities (ie, NCI Comorbidity Index of 0 and >0), because the coexistence of cancer and other conditions often have implications for treatment decisions.[24] In the second analysis, we stratified the men with and without visceral or bone metastases. This was because the study population of the LATITUDE trial consisted of men with high-risk mHSPC, and high risk is mainly defined by the status of visceral or bone metastases.[7]

Sensitivity Analyses

We performed 8 sensitivity analyses to test the robustness of the analysis. First, we included prostate-specific antigen (PSA) level as an additional covariate; it was not included in the primary analysis because nearly half of the men lacked this information. Second, we excluded the men who received no first-line treatments during follow-up in order to increase the sensitivity of identifying treatment recipients. Third, we only examined men aged ≥65 years in order to account for the unobserved confounder of insurance status, because most men in this age group are covered by Medicare. Fourth, we formed the age groups using the cutoff of 75 years. Fifth, we used 9 months as the follow-up period to define the first-line treatment period (base case: 12 months). Sixth, we used 6 months as the follow-up period (base case: 4 months) to define combination therapy. Seventh, we specified an unstructured correlation matrix for the GEE model. Finally, we fitted a complementary log-log GEE model.

Results

Study Sample

The study sample consisted of 6,888 men with newly diagnosed mHSPC with 12,738 observations who met the eligibility criteria (Figure 1). Of the sample observations, 46% were aged <70 years, and the mean age was 71 years (interquartile range, 65–77 years). Table 1 shows the characteristics of the observations in the sample, stratified by age group. The proportion of men with visceral metastases and the mean number of metastatic sites were similar between the 2 age groups. In contrast, the younger group had a higher proportion of African American/Black men, a higher proportion of men living in the Midwest and West, a lower

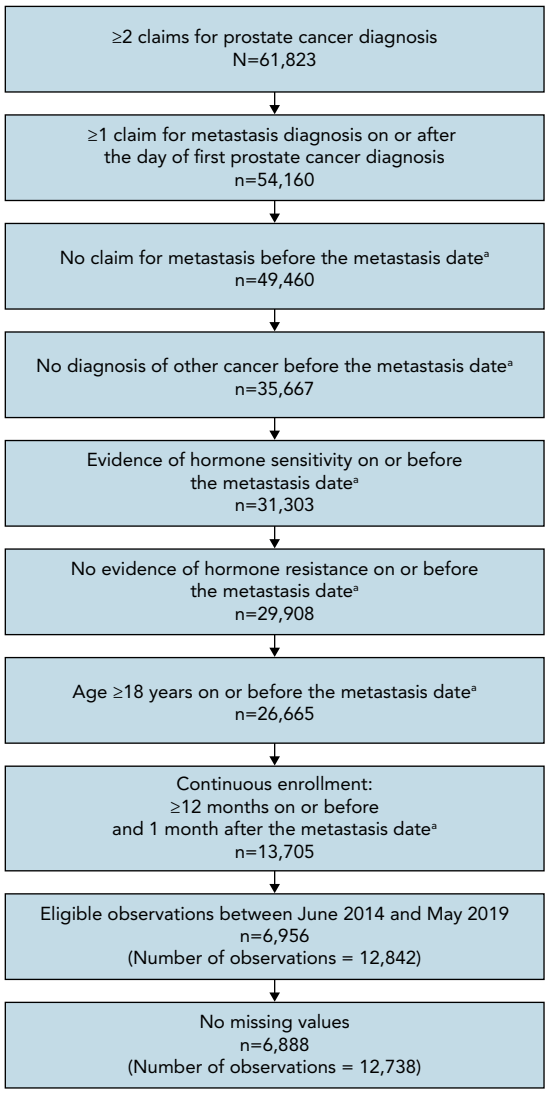

Figure 1. Flowchart of sample selection. The identification of men with metastatic hormone-sensitive prostate cancer was based on the algorithm developed by Freedland et al.[21]
[a]Metastasis date refers to the date of first claim for metastasis on or after the day of first prostate cancer diagnosis.

Table 1. Patient Sample Characteristics

Characteristic	All	Age <70 y	Age ≥70 y	*P* Value[a]
Age, mean [SD], y	71 [9]	63 [5]	78 [5]	
Race				<.001
African American/Black	19%	24%	14%	
White	71%	66%	76%	
Other[b]	10%	10%	10%	
Region				<.001
Midwest	18%	19%	17%	
Northeast	19%	18%	20%	
South	41%	40%	42%	
West	22%	23%	21%	
With bone metastases	61%	55%	66%	<.001
With visceral metastases	16%	16%	16%	.327
Number of metastatic sites, mean [SD]	2 [1]	2 [1]	2 [1]	.829
NCI Comorbidity Index, mean [SD]	0.67 [0.77]	0.54 [0.69]	0.78 [0.82]	<.001

[a]*P* values were calculated from statistical tests comparing means (*t* test) or proportions (chi-square test) of the variables between the age groups.
[b]American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, and unknown.

proportion of men with bone metastases, and a lower mean comorbidity score.

Primary Results

Unadjusted trends in AAP usage by time are provided in Figure 2. Over the 1 year before publication of the RCTs, uptake rates of AAP among men with newly diagnosed mHSPC aged ≥70 years were slightly higher than among those aged <70 years, whereas there was no evidence of differential trends. After publication, younger men experienced a more rapid increase in AAP usage. This increase commenced before the FDA announced approval in February 2018. The uptake rate among younger men surpassed older men over the entire postpublication study period.

The adjusted DID estimates of the association between publication of the RCTs and differential AAP usage groups presented a similar pattern (Figure 2). Each point indicates the adjusted DID estimate, representing the difference in AAP uptake rate between the 2 groups in each period relative to the difference in the reference period. The joint test showed that the prepublication adjusted DID estimates were not significantly different from null (*P*=.523), adding support to the assumption of parallel trends. The publication was associated with a 3.5% higher adjusted uptake rate among men aged <70 years than among those aged ≥70 years during the first postpublication period (95% CI, 1.2%–5.8%; *P*=.003). This DID estimate reflects nearly 3 times higher relative to the uptake rate that would have been expected had younger men followed the same trend as older men. The estimates plateaued throughout the observed postpublication period. The unadjusted uptake rates and adjusted DID estimates can also be found in supplemental eTable 7.

Secondary Analyses

Figure 3 shows the estimates from the 2 secondary stratified analyses. The association between the publication and the age-based differential uptake remained significant and consistent for men with comorbidities or those with visceral or bone metastases. The adjusted relative uptake rate was 4.4% among younger versus older men with comorbidities during the first postpublication period (95% CI, 1.1%–7.6%; *P*=.009). Similarly, the adjusted relative uptake rate was 4.5% among younger versus older men with visceral or bone metastases (95% CI, 1.5%–7.4%; *P*=.003). The DIDs for men without comorbidities and those without visceral or bone metastases were not statistically significant over most of the postpublication period. The details of these estimates are displayed in supplemental eTable 8.

Sensitivity Analysis

The magnitude of the association remained consistent across the sensitivity analyses, except that it would be attenuated for the last period, from December 2018 to May 2019, if excluding the observations of age <65 years or dichotomizing the age group at 75 years (supplemental eFigure 1). In addition, the estimates turned out to be less precise when we dropped observations without PSA information or men never receiving treatments during the follow-up.

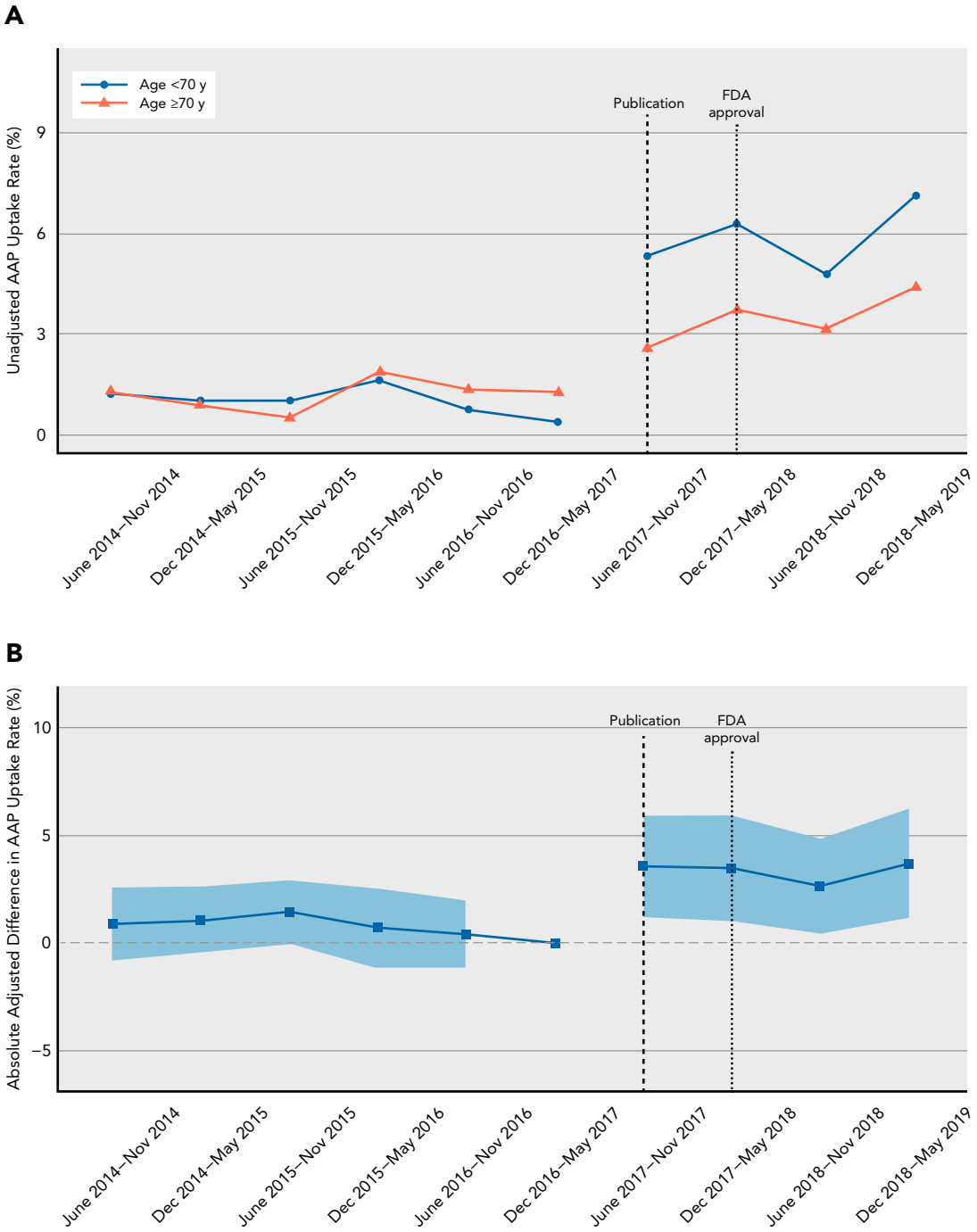

Figure 2. **(A)** Unadjusted trends and **(B)** adjusted DID estimates of the association between the publication of clinical trial results and differential uptake of AAP between younger and older men with metastatic hormone-sensitive prostate cancer.
Abbreviations: AAP, abiraterone acetate + prednisone; DID, difference-in-differences.

Discussion

In this DID event study of men with newly diagnosed mHSPC in the United States, we found that publication of pivotal RCT results was significantly associated with differential usage of AAP between age groups. Immediately after publication, the uptake rate of AAP dramatically increased among younger men—of which the estimate was approximately 3 times higher in relative terms—than what would have been expected had this group followed the same usage trends as older men. Our findings lend empirical support to the view that the information about treatment effect heterogeneity drawn from comparative

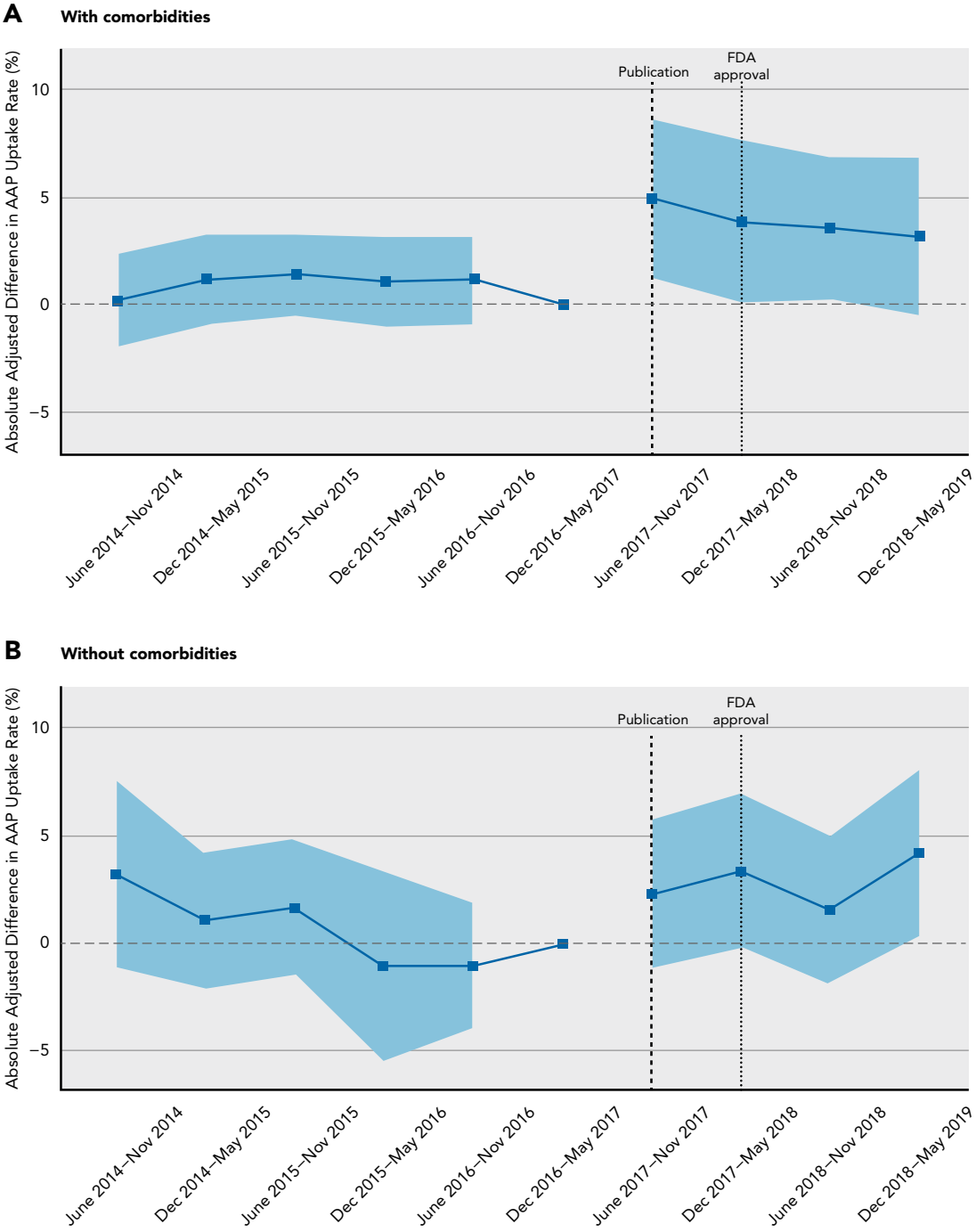

Figure 3. Adjusted DID estimates of the association between the publication of clinical trial results and differential uptake of AAP between younger and older men with metastatic hormone-sensitive prostate cancer, stratified by status of **(A, B)** comorbidities.
Abbreviations: AAP, abiraterone acetate + prednisone; DID, difference-in-differences.

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effectiveness research can induce treatment selection.[6,25] Such evidence-driven treatment selection would have substantial implications for policymaking.

Our study suggests that evidence-driven treatment selection may exist in clinical practices, despite the absence of specific clinical guidance. For example, the NCCN Guidelines do not explicitly distinguish their recommendations based on age.[26] Similarly, although the FDA cautioned about some older men's sensitivity in the label of Zytiga (abiraterone acetate),[27] the subgroup

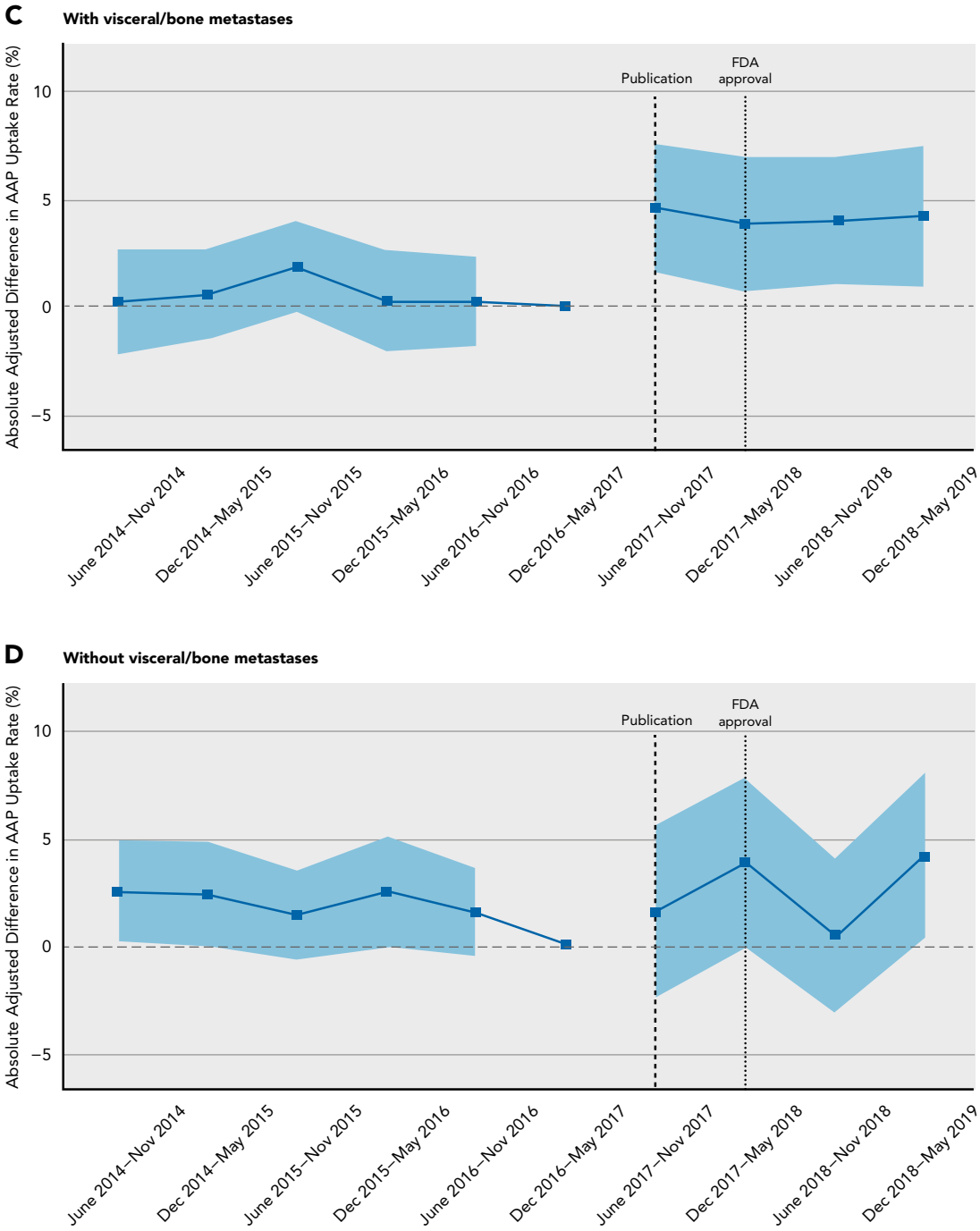

Figure 3 (cont.). Adjusted DID estimates of the association between the publication of clinical trial results and differential uptake of AAP between younger and older men with metastatic hormone-sensitive prostate cancer, stratified by status of **(C, D)** visceral/bone metastases.
Abbreviations: AAP, abiraterone acetate + prednisone; DID, difference-in-differences.

analysis finding was not mentioned. It is also worth noting that the swift, differential increase in AAP usage was observed even before FDA announced the approval. This decentralized treatment decision-making occurring in clinical practice may have critical implications for the value assessment of AAP and insurance policies. For example, the National Institute for Health and Care Excellence in the United Kingdom recommended against using AAP to treat mHSPC following the unfavorable conclusion of cost-effectiveness analysis, for which the average treatment effect estimate from the RCTs served as the cornerstone.[28] A more favorable conclusion for AAP might be expected if the

analysis accounted for the results of age subgroup analyses and the ensuing treatment selection.

However, the uncertainties of subgroup analyses in RCTs warrant caution, even though such analyses appear to be valuable for guiding personalized treatment decisions. It is widely acknowledged that subgroup analyses have nonnegligible drawbacks, such as reduced power due to small sample size and inflated true-positive rate resulting from multiple testing, which could cause bias in medical decision-making.[29–31] Especially in the case of AAP, the size of the older group was small in both the LATITUDE and STAMPEDE trials. If AAP's true treatment effect estimate was instead clinically meaningful for older men, current prescription patterns would lead to considerable health loss for them. A previous study highlighted the poor survival outcome among older men with newly diagnosed metastatic prostate cancer in the United States, manifesting a concern that they were undertreated with novel therapies such as AAP.[32] This concern underscores the importance and value of a future confirmatory study,[33] which can be a useful approach to generate a more rigorous treatment effect estimate for the specific subpopulation.

The secondary analyses found that the age-related treatment pattern remained among men with comorbidities or those with bone or visceral metastases, whereas it became unclear among men without those conditions. These exploratory analyses imply that the factor of older age, combined with other conditions, might further affect treatment decisions.[34] However, there was a relatively small number of observations without comorbidities or bone and visceral metastases in our data, which might impact the robustness of these analyses. Future studies may leverage larger data or sophisticated algorithms (eg, machine learning) to better understand how various clinical conditions together with age influence treatment selection.

Previous studies analyzing real-world data have described treatment patterns for mHSPC. Two recently published studies by Ryan et al[35] and Freedland et al[36] showed an increase in AAP usage since 2017, which agrees with the general trend found in our study. However, we found that overall usage of AAP was slightly lower in our cohort. There are 2 possible explanations for this discrepancy. First, Ryan et al[35] reported their uptake rate as the proportion of men receiving AAP in their sample stratified by the year of first metastasis diagnosis, and Freedland et al[36] reported the proportion of AAP use among all men receiving therapy in the year they evaluated. Moreover, both studies focused on individuals with insurance coverage, which differs from our cohort that includes both insured and uninsured men. Additionally, one study summarized the annual pattern by age (<75 vs ≥75 years) among Medicare beneficiaries.[37] Although their study design is distinct from ours in several ways (eg, database, data structure, uptake rate definition, treatment category, and time unit), their estimates revealed a possible faster increase in the uptake of novel hormonal therapies among younger men after 2016.

The strengths of this study include the use of nationwide EMR data for both insured and uninsured patients; the implementation of a sensitive, comprehensive algorithm to identify men with mHSPC; and the adoption of a rigorous causal inference model to control for secular usage trends. Nonetheless, our study is subject to several limitations. First, the results of the 2 clinical trials were published in 2017, and therefore the postpublication period is somewhat limited. Second, certain clinical condition variables related to prostate cancer, such as PSA level and Gleason score, were not included in the primary analysis because this information was missing for virtually half of the sample. The estimates were, however, similar when we included PSA level as a covariate in the sensitivity analysis. Finally, even though we controlled several demographic variables, there potentially exist unobserved confounders. Insurance status is a typical example, because uninsured patients are less likely to afford abiraterone. However, adjusting for insurance would magnify the DID estimates because the younger group has a higher number of uninsured individuals. Moreover, the sensitivity analysis restricting to men aged ≥65 years, who are predominantly covered by Medicare, did not produce substantially different results.

Conclusions

Despite the absence of clinical guidance for differential use of AAP to treat mHSPC between age groups, our study found a significantly faster increase in AAP uptake among younger than older men after publication of the pivotal RCTs. Our study highlights the importance of a future confirmatory study among older men, considering the nonnegligible uncertainties of subgroup analyses in RCTs.

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Supplemental online content for:

Does Clinical Evidence of Heterogeneity Impact Treatment Selection? A Case Study of Abiraterone for Metastatic Prostate Cancer

Boshen Jiao, PhD, MPH; Yaw A. Nyame, MD, MS, MBA; Josh J. Carlson, PhD, MPH; Louis P. Garrison Jr, PhD; and Anirban Basu, PhD

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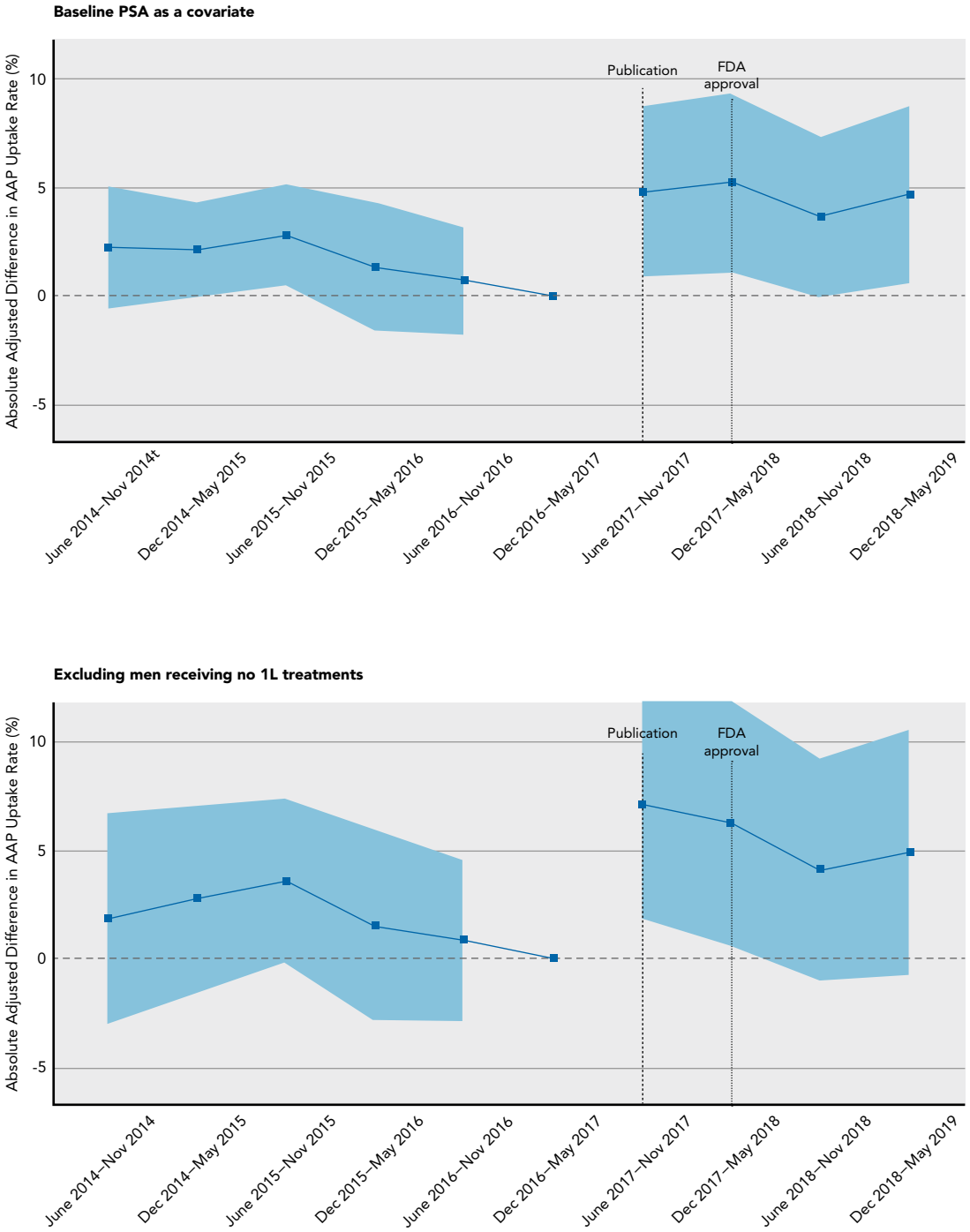

eFigure 1. Adjusted difference-in-differences estimates in sensitivity analyses.
Abbreviations: 1L, first-line; AAP, abiraterone acetate + prednisone; PSA, prostate-specific antigen.

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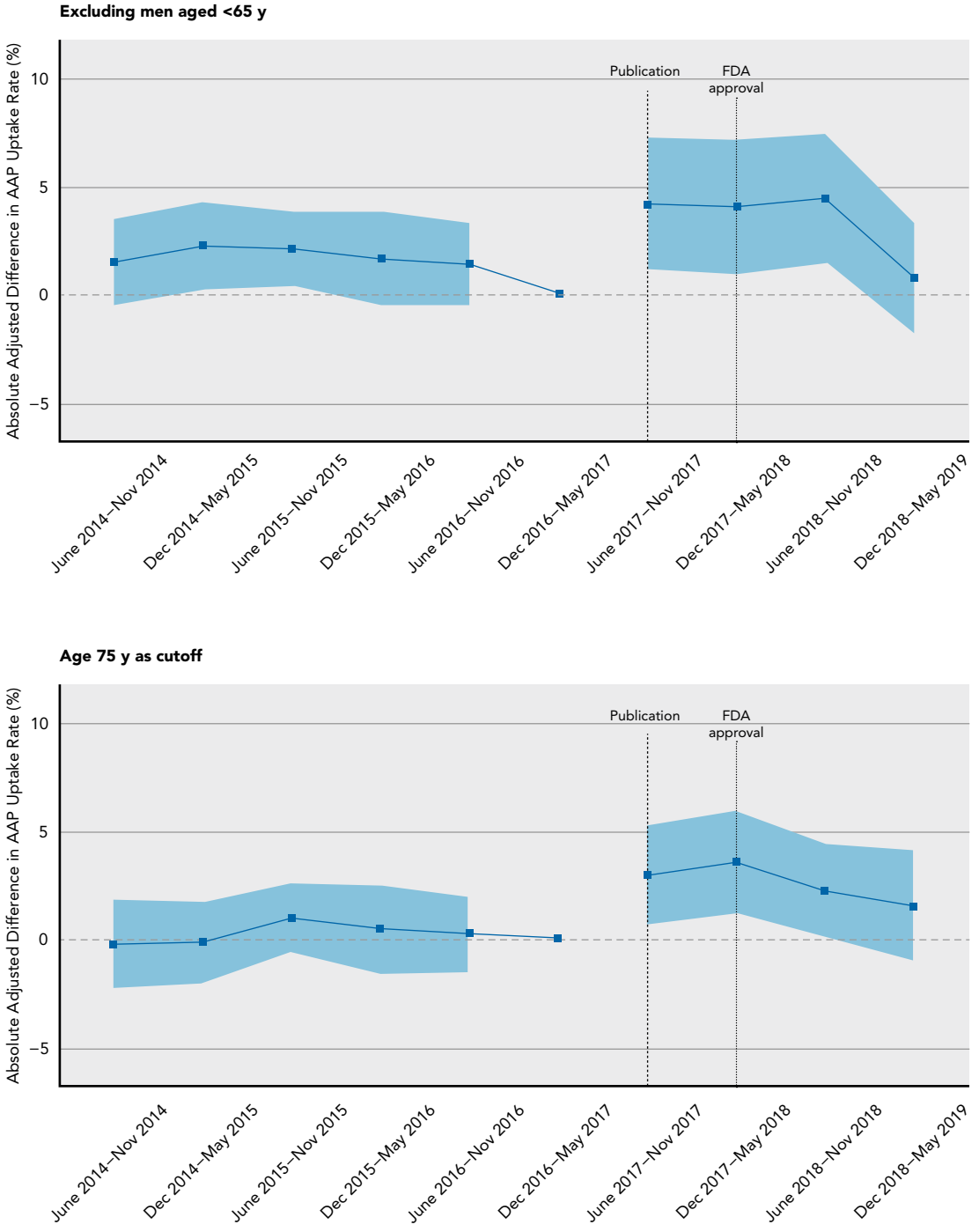

eFigure 1 (cont.). Adjusted difference-in-differences estimates in sensitivity analyses.
Abbreviations: 1L, first-line; AAP, abiraterone acetate + prednisone; PSA, prostate-specific antigen.

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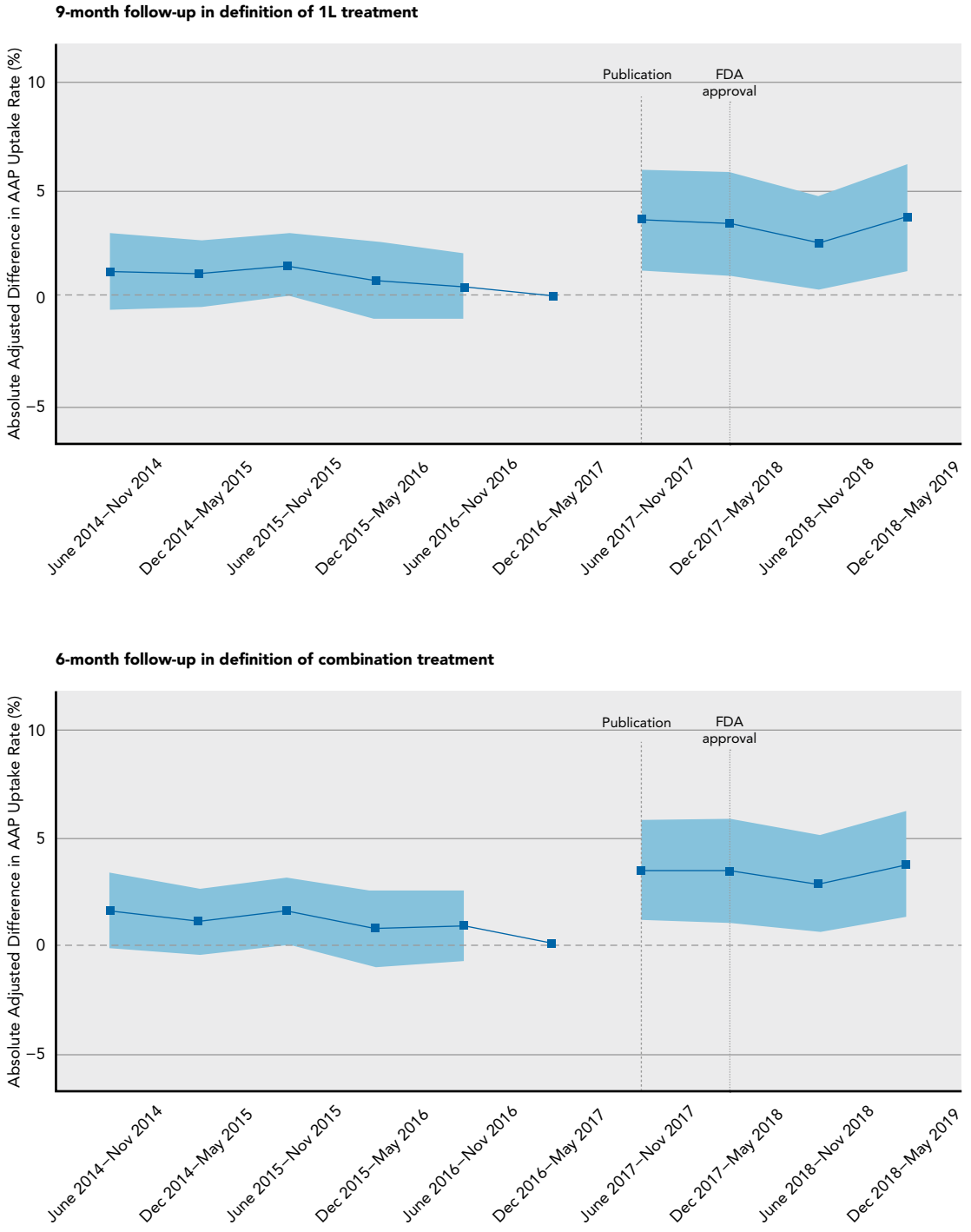

eFigure 1 (cont.). Adjusted difference-in-differences estimates in sensitivity analyses.
Abbreviations: 1L, first-line; AAP, abiraterone acetate + prednisone; PSA, prostate-specific antigen.

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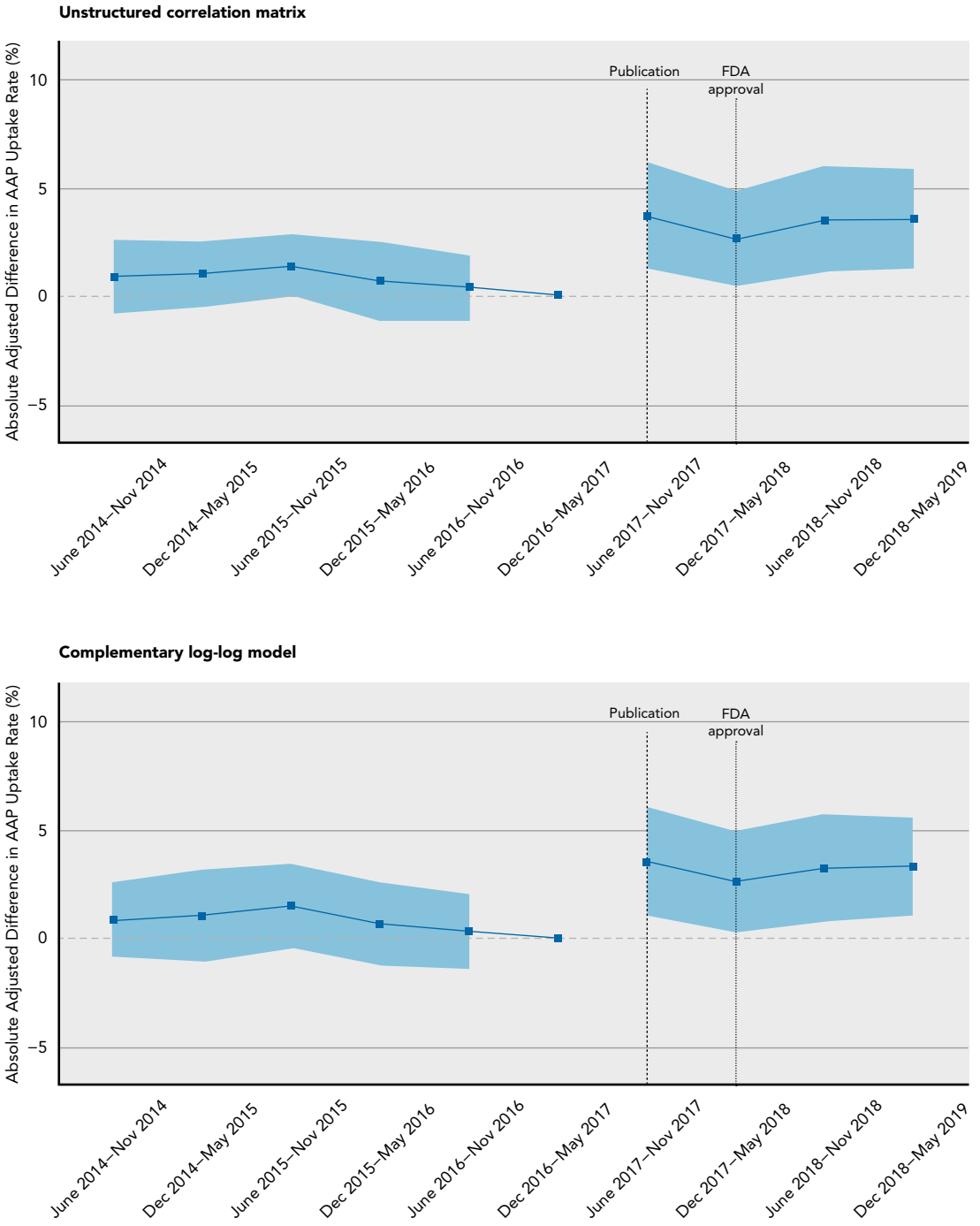

eFigure 1 (cont.). Adjusted difference-in-differences estimates in sensitivity analyses.
Abbreviations: 1L, first-line; AAP, abiraterone acetate + prednisone; PSA, prostate-specific antigen.

eTable 1. Algorithm to Identify Men With Newly Diagnosed Metastatic Hormone-Sensitive Prostate Cancer With ICD Codes

	Criteria (all must be met)	Details	ICD-9-CM	ICD-10-CM
1	Prostate cancer diagnosis	≥2 claims for prostate cancer diagnosis during the study period	185	C61
2	Metastasis diagnosis on or after first observed prostate cancer diagnosis	≥1 claim for metastatic disease diagnosis on or after the day of first prostate cancer diagnosis (metastasis date is defined as the date of the first claim)	196.xx–199.1, 209.7x	C77.xx–C80.0, C7B
3	No metastasis diagnosis prior to the metastasis date	No claims for a diagnosis of metastatic disease prior to the metastasis date	196.xx–199.1, 209.7x	C77.xx–C80.0, C7B
4	No other cancers prior to the metastasis date	No claims with a diagnosis of metastatic disease prior to the metastasis date	140–165, 170–176, 179–184, 186–195, 199, 200–209.3, 258.0, 789.51	C00–C26, C30–C58, C60, C62–C76, C80–C96, C7A, C7B, E31.20–E31.23, R18.0
5	Information required to assess hormone sensitivity on or prior to the metastasis date	Information required to assess hormone sensitivity on or prior to the metastasis date	See eTable 2	See eTable 2
6	No prior evidence of castration resistance	No evidence of hormone resistance on or prior to the metastasis date	See eTable 2	See eTable 2
7	Adult age	Age ≥18 years on the metastasis date	—	—
8	Minimum baseline period	≥12 months of continuous enrollment prior to the metastasis date	—	—
9	Minimum follow-up period	≥1 month of follow-up to the metastasis date (including the first metastasis date)	—	—

eTable 2. Criteria for Identifying Hormone Sensitivity and Resistance With With ICD, CPT, and HCPCS Codes

	Criteria for the Identification of Hormone Sensitivity	Details	Codes
1	Based on ICD-10-CM code	≥1 diagnosis code indicating hormone-sensitive malignancy status within 12 months prior to or on the date of the first observed metastasis diagnosis	**Hormone-sensitive status** ICD-10-CM Z19.1 – Hormone-sensitive malignancy status
2	Based on surgical castration and PSA	≥1 claim for surgical castration at any time point prior to the date of the first observed metastasis diagnosis AND ≥2 PSA test results following the surgical castration and within 12 months prior to or on the date of the first observed metastasis diagnosis	**Surgical castration** ICD-9-CM 62.3, 62.41, 62.42, V45.77 ICD-10-CM Z90.79 ICD-10-PCS 0VT90ZZ, 0VTB0ZZ CPT 54520, 54521, 54522, 54530, 54535, 54690, 49510 **PSA test** CPT 84152, 84153, 84154 HCPCS G0103, G9080
3	Based on medical castration and PSA	Medical castration (ie, ≥1 episode of 90 days of continuous ADT) prior to the date of the first observed metastasis diagnosis AND ≥2 PSA test results during an episode of ≥90 days of continuous ADT use and within 12 months prior to or on the date of the first observed metastasis diagnosis	**Medical castration (leuprolide, triptorelin, goserelin, histrelin, degarelix, relugolix)** NDC and RxNorm See eTable 3 HCPCS J9202, J1950, J9217, J9218, J9219, J3315, J9226, J1695, J9225, J9226, J1675 **PSA test** See above
4	Based on hormone/castration naïveté	Hormone/Castration naïve, defined as no claim for surgical castration prior to the date of the first observed metastasis diagnosis and no claim for ADT in the 18 months prior to the date of the first observed metastasis diagnosis (only patients with ≥18 months continuous enrollment prior to the date of the first observed metastasis diagnosis were considered)	**Surgical castration** See above **Medical castration (leuprolide, triptorelin, goserelin, histrelin, degarelix, relugolix)** See above
	Criteria for the Identification of Hormone Resistance	**Details**	**ICD-10-CM**
1	Based on ICD-10-CM code	≥1 diagnosis code indicating hormone resistance during the study period	**Hormone resistance status** ICD-10-CM Z19.2 – Hormone-resistant malignancy status
2	Based on surgical castration and PSA	≥1 claim for surgical castration at any time point (across all years where data are available), **AND** ≥2 PSA test results (including one nadir and one postnadir [ie, the lowest PSA value observed postsurgical castration]) after the surgical castration AND ≥1 increase in PSA (of ≥25% with an absolute increase of ≥2 ng/mL) after nadir, indicating resistance **OR** ≥1 diagnosis code indicating increasing PSA following treatment of malignant neoplasm of prostate, after the surgical castration	**Surgical castration** See above **PSA test** ICD-10-CM R97.21
3	Based on increasing PSA following medical castration	Medical castration (ie, ≥1 episode of ≥90 days of continuous ADT) during the study period, **AND** ≥2 PSA test results (including one nadir [ie, the lowest observed PSA value in a given episode of ≥90 days of continuous ADT use] and one postnadir) within the same episode of continuous ADT AND ≥1 increase in PSA (of ≥25% with an absolute increase of ≥2 ng/ mL) after nadir while on the same episode of continuous ADT use, indicating resistance **OR** ≥1 diagnosis code indicating increasing PSA following treatment of malignant neoplasm of prostate, during a continuous ADT episode	**Medical castration (leuprolide, triptorelin, goserelin, histrelin, degarelix, relugolix)** See above **PSA test** See above

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eTable 2. Criteria for Identifying Hormone Sensitivity and Resistance With With ICD, CPT, and HCPCS Codes (cont.)

	Criteria for the Identification of Hormone Resistance	Details	ICD-10-CM
4	Based on initial metastatic diagnosis occurred ≥90 days after surgical castration	Had surgical castration at least 90 days prior to the first observed metastasis diagnosis during the study period	**Surgical castration** See above
5	Based on initial metastatic diagnosis occurred after 90 days of medical castration	Had continuous ADT throughout 90 days (with no gap >30 days) prior to the first observed metastasis diagnosis during the study period	**Medical castration (leuprolide, triptorelin, goserelin, histrelin, degarelix, relugolix)** See above
6	Based on mCRPC medications	≥1 claim for drugs solely used for mCRPC	See eTable 4

Abbreviations: ADT, androgen deprivation therapy; mCRPC, metastatic castrate-resistance prostate cancer; PSA, prostate-specific antigen.

eTable 3. Medical Castration Drugs With NDC and RxNorm Codes

Agent	Brand Name	NDC	RxNorm
Leuprolide	Lupron Depot Lupron (leuprolide acetate) Fensolvi Eligard Viadur Camcevi	00024-0222, 00024-0605, 00024-0610, 00024-0793, 00074-3680, 00781-4003, 41616-0936, 47335-0936, 49884-0368, 62935-0222, 62935-0223, 62935-0302, 62935-0303, 62935-0452, 62935-0453, 62935-0752, 62935-0753, 00703-4014, 00074-3346, 00074-3473, 00074-3642, 00074-3683, 00185-7400	825334, 752899, 825325, 825335, 2371773, 752884, 752894, 825333, 752889, 1115447, 1115454, 1115457, 1115462, 1115459, 1115464, 1115449, 1115456, 1115467, 1115257, 1115472, 1115468, 1115259, 1946522, 1115473, 1946520, 1946519, 1946521, 1173874, 352619, 2371772, 2371769, 1115448, 1115446, 583426, 2371770, 583425, 583424, 1115455, 545830, 1115470, 545848, 545847, 1115458, 545843, 583436, 1115258, 583434, 545835, 545834, 583431, 583429, 1115463, 1116124, 1115461, 203217, 1163443, 372576, 378232, 825324, 2371771, 727602, 727599, 42375, 1488617, 1488619, 1181489, 203852, 1488618, 1488616
Triptorelin	Trelstar	00023-5902, 00023-5904, 00023-5906, 52544-0092, 52544-0153, 52544-0154, 52544-0156, 52544-0188, 52544-0189	905064, 905057, 905059, 1179671, 905060, 905054, 1944389, 1944388, 1944385, 1863382, 905062, 1863380, 1863378, 1944386, 905053, 1863376, 1863373, 199821, 1863370, 236538, 1159353, 1863374, 1944387, 1863371, 338529, 38782
Goserelin	Zoladex	50090-2027, 70720-0951, 70720-0950, 50090-3466, 00310-0950, 00310-0951	571914, 314008, 353411, 564142, 310592, 358339, 203146, 370482, 1156883, 379243, 50610, 211544, 105641, 1188163, 58328
Histrelin	Supprelin LA Vantas	67979-0500	1740434, 1740433, 1740432, 1740438, 1740437, 1740436, 1294622, 726764, 606384, 1159514, 597332, 50975, 1294641, 1184859, 220125, 1294626, 1187561, 606382
Degarelix	Firmagon	55566-8303, 55566-8403, 55566-8301, 55566-8401	1812347, 828751, 1812344, 1812352, 828749, 1812350, 835863, 1157202, 1812348, 1812345, 475230, 858127, 858125, 1169000, 858122
Relugolix	Orgovyx	72974-0120	2556802, 2556805, 2556797, 2556801, 2556806, 2556799, 2556798, 2556800, 2556804, 2556795, 2556803, 2472789, 2472787, 2472788, 2472784, 2472785, 2472783, 2472779, 2556796, 2472780, 2472786, 2472782, 2472781, 2472778

eTable 4. Drugs Only for Metastatic Hormone-Resistant Prostate Cancer With NDC, RxNorm, and CPT Codes

Agent	Brand Name	NDC	RxNorm	CPT
Diethylstilbestro	Stilboestrol	—	690681, 204498, 315810, 204499, 317353, 1151502, 1151503, 371825, 1151504, 3390	—
Estramustine phosphate	Emcyt Estracyt	00013-0132	205562, 1175302, 1175303, 3815, 566462, 310194, 330431, 366197, 372082, 1165764, 4090, 1165765, 4089	—
Polyestradiol phosphate	Estradurin Estradurine	—	34120, 34119	—
Cabazitaxel	Jevtana	00024-5824	1001433, 1376083, 1001432, 1164944, 1812334, 1812332, 996051,1376084,1167866, 996055	—
Mitoxantrone	Novantrone	00069-0080, 00703-4680, 00703-4685, 00703-4686, 55390-0083, 55390-0084, 55390-0085, 61703-0343, 63323-0132	197989, 328493, 203129, 1165375, 375173, 7005	J9293
Cisplatin	Platinol Platinol-AQ	00015-3070, 00015-3072, 00069-0081, 00069-0084, 00703-5747, 00703-5748, 16729-0288, 16729-0288, 44567-0509, 44567-0510, 44567-0511, 44567-0530, 47781-0609, 47781-0610, 61126-0003, 61126-0004, 63323-0103, 67457-0424, 67457-0425, 68001-0283, 68083-0162, 68083-0163, 70860-0206	309311, 328303, 1736854, 1736852, 1152129, 376433, 1736853, 2555	J9060
Etoposide	Etoposide Etopophos Toposar	00015-3404, 00378-3266, 00703-5653, 00703-5656, 00703-5657, 16729-0114, 16729-0262, 55390-0291, 55390-0292, 55390-0293, 55390-0491, 55390-0492, 55390-0493, 63323-0104, 68001-0265	226719, 1734344, 274342, 1734342, 1734340, 199315, 329753, 567639, 310248, 315912, 197687, 315913, 1157928, 362881, 376890, 1734343, 1734339, 372132, 1157929, 24614, 1157930, 4179, 206831 1178005, 220347	—
Pembrolizumab	Keytruda	00006-3026, 00006-3029	1657750, 1657751, 1657749, 1547553, 1547550, 1547551, 1547546, 1657747, 1657746, 1657744, 1547547, 1657748, 1657745, 1547545	—
Sipuleucel-T	Provenge	30237-8900	997264, 997267, 1182470, 978086, 997265, 997262, 1159660, 1726183, 1726181, 997261	Q2043
Radium-223	Xofigo	50419-0208	1424214, 1745393, 1745391, 1424212, 1745387, 1745384, 1424174, 1424219, 1424218, 1424215	A9606

eTable 5. Drugs for Both Metastatic Hormone-Sensitive and -Resistant Prostate Cancer With NDC, RxNorm, and CPT Codes

Agent	Brand Name	NDC	RxNorm	CPT
Abiraterone acetate	Zytiga Yonsa	0093-1125-89, 0143-9597-21, 0378-6920-78, 0378-6921-91, 0378-6924-37, 0904-6948-04, 16714-963-01, 42291-024-12, 42291-073-60, 42292-057-03, 43598-358-04, 47335-401-81, 51407-181-12, 57894-150-12, 57894-155-12, 57894-195-06, 57894-195-15, 60505-4327-1, 60505-4327-3, 60687-455-21, 64679-021-01, 64980-418-12, 68001-489-07, 68462-135-08, 69238-1165-7, 69238-1754-6, 69539-049-92, 72205-030-92, 72606-566-01	2046581, 2046579, 2046578, 1100077, 1100075, 1100073, 1918043, 1918042, 1918041, 1100071, 1163656, 2046582, 1100078, 1100074, 1163657, 1100072, 2046585, 2046583, 2046584, 2046580, 1100079, 1918044, 1186683, 1186684, 1100076	—
Docetaxel	Docefrez Taxotere	00075-8003, 00075-8004, 00075-8005, 00409-0366, 00409-0367, 00409-0368, 00703-5720, 00703-5730, 00955-1020, 00955-1021, 00955-1022, 16714-0465, 16714-0500, 16729-0231, 16729-0267, 25021-0222, 39822-2120, 39822-2180, 39822-2200, 42367-0121, 43598-0258, 43598-0259, 43598-0610, 43598-0611, 45963-0734, 45963-0765, 45963-0781, 45963-0790, 57884-3021, 63739-0932, 63739-0971, 66758-0050, 66758-0950, 25021-0245, 47335-0285, 50742-0428, 50742-0431, 50742-0463, 16729-0120, 16729-0228, 70121-1221, 70121-1222, 70121-1223, 43066-0001, 43066-0006, 43066-0010, 00069-9141, 00069-9142, 00075-8001, 00409-0201, 00069-9144, 00409-0369, 67457-0531, 67457-0532, 67457-0781, 69097-0369, 69097-0371, 00143-9204, 00143-9205, 43598-0389, 47335-0323, 47335-0895, 47335-0939, 72485-0216, 72485-0215, 72485-0214, 71288-0143, 71288-0144, 71288-0150, 71288-0151, 00409-7870, 00409-0365, 00409-1732, 00409-4235, 00409-5068, 55150-0378, 55150-0379, 55150-0380, 68083-0401, 68083-0400, 68083-0399, 70700-0176, 70700-0175, 70700-0174	1870937, 1860480, 1860482, 1918045, 1860619, 1860485, 1860486, 1861411, 1101773, 1111073, 1173805, 1101770, 1093280, 1093279, 1001406, 1001405, 1001404, 1101771, 1101769, 1101768, 1111072, 1111071, 1111070, 329054, 1299922, 1160617, 1101772, 376888, 1860481, 1860479, 72962, 1180259, 202982	J9171
Enzalutamide	Xtandi	00469-0125, 00469-0625, 00469-0725	1307305, 1307303, 2390644, 1307299, 2390649, 2390648, 2390647, 1307306, 1307302, 1307300, 2390645, 2390643, 1307301, 1307298, 1307309, 2390646, 2390650, 1307307, 1307308, 1307304	—
Apalutamide	Erleada	59676-0600	1999583, 1999581, 1999577, 1999578, 1999584, 1999580, 1999579, 1999574, 1999587, 1999585, 1999586, 1999582	—
Bicalutamide	Casodex	00904-6019, 16729-0023, 41616-0485, 42291-0168, 47335-0485, 51079-0692, 51991-0560, 54868-4503, 54868-6133, 60429-0177, 60429-0226, 60505-2642, 63629-5321, 63672-0005, 65841-0613, 67253-0191, 68084-0374, 69189-0298, 16714-0571, 16714-0816, 62559-0680, 00378-7017, 00781-5409, 68084-0612, 00093-0220, 00310-0705, 52125-0709, 68382-0224, 62559-0890, 70518-2993	349406, 350633, 564608, 199123, 315478, 1161189, 369055, 371070, 1161190, 83008, 108828, 1175807, 1175808, 151495	—
Flutamide	Eulexin	00185-1125, 00555-0870, 49884-0753, 54868-4628, 55567-0150, 60429-0272, 69097-0915, 00172-4960, 00591-2466	197726, 315960, 199609, 332500, 372251, 1161458, 372252, 1161459, 4508	—
Nilutamide	Nilandron	24987-0111, 59212-0111, 62559-0173, 00088-1111, 66993-0212	284551, 1183905, 1183906, 218741, 574979, 311982, 331558, 1158946, 367745, 373082, 1158947, 31805	—

eTable 6. Inclusion and Exclusion Criteria to Identify Proportion of Men Initiating First-Line AAP During a Given Period

	Numerator	Denominator
Inclusion criteria	All must be met: • AAP was initiated during the period ➤ AAP initiation date is the index date • ADT was initiated within 4 months before or 1 month after the index date • Metastasis was diagnosed within 12 months before or 3 months after the ADT initiation	At least one must be met: • Metastasis was diagnosed within 12 months before or during the period • ADT was initiated within 4 months before or during the period, and metastasis was diagnosed within 12 months before or 3 months after the ADT initiation • Any add-on therapy was initiated during the period, ADT was initiated within 1 month after the add-on therapy initiation, and metastasis was diagnosed within 12 months before or 3 months after the ADT initiation
Exclusion criteria	At least one must be met: • Another add-on therapy (docetaxel or first-generation antiandrogen) was initiated before the index date • Disease progressed before the index date ➤ Disease progression was identified by the use of any drug only indicated for metastatic hormone-resistant cancer or diagnosis code for hormone resistance	At least one must be met: • ADT was initiated >4 months before the period • Any add-on therapy was initiated before the period • Disease progressed before the period • Patients dropped out or died before the period

Abbreviations: AAP, abiraterone acetate + prednisone; ADT, androgen deprivation therapy.

eTable 7. Number of Men at Risk for Initiating AAP, Unadjusted Uptake Rate of AAP, and Adjusted DID Estimates During Each Time Period in Primary Analysis

Time Period	Men at Risk, n (Age <70 y)	Men at Risk, n (Age ≥70 y)	Unadjusted Uptake Rate (Age <70 y)	Unadjusted Uptake Rate (Age ≥70 y)	Adjusted DID Estimate (95% CI)
June 2014–Nov 2014	492	553	1.22%	1.27%	0.88% (−0.82% to 2.57%)
Dec 2014–May 2015	505	579	0.99%	0.86%	1.04% (−0.50% to 2.58%)
June 2015–Nov 2015	489	605	1.02%	0.50%	1.42% (−0.04% to 2.89%)
Dec 2015–May 2016	553	587	1.63%	1.87%	0.71% (−1.10% to 2.52%)
June 2016–Nov 2016	539	599	0.74%	1.34%	0.40% (−1.13% to 1.93%)
Dec 2016—May 2017	550	629	0.36%	1.27%	—
June 2017–Nov 2017	601	739	5.32%	2.57%	3.53% (1.20% to 5.85%)
Dec 2017–May 2018	668	829	6.29%	3.74%	3.45% (1.00% to 5.89%)
June 2018–Nov 2018	690	891	4.78%	3.14%	2.63% (0.43% to 4.83%)
Dec 2018–May 2019	730	910	7.12%	4.40%	3.65% (1.16% to 6.15%)

Abbreviations: AAP, abiraterone acetate + prednisone; DID, difference-in-differences.

eTable 8. Adjusted Difference-in-Differences Estimates During Each Time Period in Secondary Analyses

Time Period	Men Without Comorbidities	Men With Comorbidities	Men Without Visceral/Bone Metastasis	Men With Visceral/Bone Metastasis
June 2014–Nov 2014	3.21% (−1.04% to 7.47%)	0.18% (−1.70% to 2.06%)	2.41% (0.06% to 4.75%)	0.20% (−2.23% to 2.62%)
Dec 2014–May 2015	1.10% (−2.04% to 4.24%)	1.04% (−0.84% to 2.91%)	2.29% (−0.09% to 4.67%)	0.52% (−1.54% to 2.58%)
June 2015–Nov 2015	1.69% (−1.41% to 4.79%)	1.27% (−0.48% to 3.02%)	1.34% (−0.71% to 3.39%)	1.78% (−0.31% to 3.88%)
Dec 2015–May 2016	−0.99% (−5.34% to 3.36%)	0.96% (−0.92% to 2.84%)	2.42% (−0.10% to 4.95%)	0.27% (−2.07% to 2.61%)
June 2016–Nov 2016	−0.96% (−3.79% to 1.87%)	1.03% (−0.81% to 2.88%)	1.47% (−0.55% to 3.48%)	0.20% (−1.83% to 2.24%)
Dec 2016–May 2017	—	—	—	—
June 2017–Nov 2017	2.31% (−1.14% to 5.76%)	4.36% (1.07% to 7.65%)	1.46% (−2.52% to 5.44%)	4.47% (1.54% to 7.40%)
Dec 2017–May 2018	3.34% (−0.20% to 6.87%)	3.42% (0.03% to 6.82%)	3.72% (−0.14% to 7.58%)	3.74% (0.65% to 6.83%)
June 2018–Nov 2018	1.55% (−1.86% to 4.96%)	3.16% (0.20% to 6.12%)	0.41% (−3.09% to 3.91%)	3.87% (1.00% to 6.75%)
Dec 2018–May 2019	4.18% (0.35% to 8.00%)	2.82% (−0.47% to 6.11%)	4.03% (0.27% to 7.79%)	4.11% (0.88% to 7.35%)

eAppendix 1. Statistical Model

We observed whether patient i initiated the first-line treatment in period t. Let the period $t = -1$ be the reference period, which indicates the first 6 months before the online publication of trials' results (ie, December 2016 to May 2017). Our sample included the $t = -1, \ldots, -6$ periods before the publication, and $t = 1, \ldots, 4$ periods after the publication. The statistical model is constructed as follows:

$$Y_{it} = \alpha_t + \sum_{s \neq -1} \beta_s \times G_t \times 1[t = s] + \beta_g \times G_t + \gamma + \delta_t + \epsilon_{it}$$

where Y_{it} is a binary outcome variable indicating whether man i initiated the first-line AAP or not in period t, α_t indicates time fixed effect, G_t indicates the group of men aged <70 years, γ represent time-independent variables, and δ_t represent the time-varying variables, α is the intercept, and β_s denotes the vector of coefficients for the interactions between the fixed time effects and age group indicator.

Reference

1. Freedland SJ, Ke X, Lafeuille MH, et al. Identification of patients with metastatic castration-sensitive or metastatic castration-resistant prostate cancer using administrative health claims and laboratory data. Curr Med Res Opin 2021;37:609–622.